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PATENT APPLICATION
09/444,459

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPEAL FROM THE EXAMINER TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	Bruce M. Cameron Sr. et al.
Serial No.:	09/444,459
Filing Date:	November 22, 1999
Group Art Unit:	1654
Examiner:	Leary, Louise N
Title:	***Methods and Compositions for Pain Management***

I hereby certify that this communication is being deposited with the United States Postal Service as Express Mail **EV341125652US** addressed to: Mail Stop Appeal Brief-Patents, Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Jay Howard

9-8-03

Date of Signature

Mail Stop Appeal Brief-Patents
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Dear Sir:

APPEAL BRIEF

Applicant has appealed to the Board of Patent Appeals and Interferences from the decision of the Examiner mailed April 8, 2003, finally rejecting Claims 56, 60-67, 70, 76, 78 and 81-85. Applicant filed a Notice of Appeal on July 8, 2003. Applicant respectfully submits this appeal brief, in triplicate, with a statutory fee of $160.00.

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REAL PARTY IN INTEREST

The present application was assigned to Proteome Sciences, Inc. and Bruce Cameron, Sr., as indicated by an assignment from the inventors recorded on March 27, 2000 in the Assignment of Records of the United States Patent and Trademark Office at Reel 010708, Frame 0323 and an assignment from Proteome Sciences, Inc. to Bruce Cameron, Sr. of 25% interest recorded on December 2, 2002 in the Assignment of Records of the United States Patent and Trademark Office at Reel 013549, Frame 0333.

Proteome Sciences, Inc. is a subsidiary of Proteome Sciences PLC, a United Kingdom corporation. Proteome Sciences PLC is also a party in interest.

RELATED APPEALS AND INTERFERENCES

There are no known appeals or interferences that will directly affect or be directly affected by or have a bearing on the Board's decision in this pending appeal.

STATUS OF CLAIMS

Claims 21-25, 56, 60-67, 69, 70, 76, 78 and 81-85 are pending. Claims 56, 60-62, 67, 76 and 81-85 stand rejected pursuant to an Office Action mailed April 8, 2003. Claims 63-66, 69, 70, 78 and 81 were objected to as dependent upon a rejected base claim. Claims 21-25 were deemed allowable. Claims 56, 60-62, 67, 76 and 81-85 are all presented for appeal.

SUMMARY OF INVENTION

The present invention involves a method of diagnosing the extent of activation of the pain sensing neurological pathway by detecting a pain marker such as cholinesterase in a biological sample from a patient. See Specification, page 8, lines 11-12. The amount of pain marker may be compared to a threshold amount of pain marker based on measurements of the marker in patients who are not in pain. See Specification, page 8, lines 12-15. In order to limit false positives, the pain sensing neurological pathway in the patient is not designated as activated in some embodiments unless the amount of cholinesterase pain marker in the patient is at least three standard deviations above the threshold amount. See Specification, page 29, lines 9-11. Cholinesterases may be detected through eserine sensitivity in some embodiments of the invention. Specification, page 26, lines 16-17.

The invention additionally involves a method of determining the efficacy of a pain treatment by comparing the amount of a pain marker in a biological sample from a patient obtained before treatment with the amount of a pain marker in a sample obtained after treatment. See Specification, page 8, line 17 to page 9, line 9.

Another method of the invention relates to identifying a marker that correlates with the intensity of pain perceived by a patient. In the method, a serum sample is collected from the patient and separated by electrophoresis in a gel. Then the gel is reacted with a diazonium salt and a substrate for a period of time to produce a detectable band that may be used to identify the marker. See Specification, page 8, lines 20-26.

Finally, the invention includes diagnostic kits for determining the level of activation of the pain sensing neurological pathway in a patient. The kit includes an agent such as an antibody that binds to cholinesterase in a sample to allow determination of the amount of cholinesterase in the sample. This amount may then be compared with an amount known to be indicative of activation of the pain sensing neurological pathway. See Specification, page 9, lines 10-15.

STATEMENT OF ISSUES

1. Whether Claims 56, 60-62, 67, 76 and 82-85 stand properly rejected under 35 U.S.C. § 102 (b) as anticipated by U.S. Patent No. 3,928,594 issued to Cook (hereinafter "Cook").

2. Whether Claims 56, 60-62, 67, 76 and 82-85 are obvious under 35 U.S.C. § 103 (a) in light of Cook.

GROUPING OF CLAIMS

Applicant requests that Claims 56, 60-62 and 67 be grouped to stand or fall together according to 37 C.F.R. § 1.192(c)(7). Applicant requests that Claim 76 not be grouped with other claims and stands or falls on its own according to 37 C.F.R. § 1.192(c)(7). Applicant requests that Claim 82 not be grouped with other claims and stands or falls on its own according to 37 C.F.R. § 1.192(c)(7). Applicant requests that Claim 83 not be grouped with other claims and stands or falls on its own according to 37 C.F.R. § 1.192(c)(7). Applicant requests that Claim 84 not be grouped with other claims and stands or falls on its own

according to 37 C.F.R. § 1.192(c)(7). Applicant requests that Claim 85 not be grouped with other claims and stands or falls on its own according to 37 C.F.R. § 1.192(c)(7).

ARGUMENT

The rejections to the claims are considered to be without merit for the reasons presented in detail below. In summary, the Examiner persists in rejecting the claims as anticipated by or obvious in light of a single reference, Cook. These rejections are based on material allegedly inherent in the reference. The Examiner's explanation of how the relevant material is inherent does not rise to the standards articulated in the Manual of Patenting Examination Procedure (MPEP) and the case law regarding an assertion of inherency.

Accordingly, all claims in this case appear to be in condition for allowance and such acknowledgment is respectfully requested from the Board of Patent Appeals and Interferences.

(1) Rejections under 35 U.S.C. § 102 (b)

a. Description of the Cook Reference and the Office Actions

Claims 56, 60-62, 67, 76 and 82-85 were rejected under 35 U.S.C. § 102 (b) as anticipated by U.S. Patent No. 3,928,594 issued to Cook (hereinafter "Cook").

Applicant respectfully traverses the § 102 rejections. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1997). Furthermore, "the identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co. Ltd.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Applicant respectfully submits that the Cook reference cited as anticipatory by the Examiner cannot anticipate the rejected Claims, because Cook does not show all the elements of the present Claims.

Cook discloses a method for treating the signs and symptoms associated with demyelination disorders, specifically multiple sclerosis, using a specific cholinesterase reactivator of the oxime class. See Cook Col. 1, lines 4-6. These disorders are characterized by an acetylcholine-cholinesterase imbalance. See Cook Col. 1, lines 7-9. Patients who

received Cook's composition were compared to those who received a placebo. See Cook, Col. 4, lines 2-5. Treatment of demyelination disorder patients with the composition disclosed in Cook resulted in improvements in alertness, mental depression, function of the voluntary motor system and ataxia. Treatment also specifically provided relief of pain. See Cook Col. 4, lines 5-41. Further, Cook states that "the significant effect in demyelinating diseases of compounds [such as the novel Cook compound] capable of changing the chemical constitution of cholinesterase suggests that a major effect in the symptomology depends upon the degree of change in the chemistry of cholinesterase. See Cook, Col. 4, lines 53-57.

However, Cook never states that he measured cholinesterase levels in his patients. Further he never indicates how he measured relief of pain other than to describe it as a "clinical effect". See Cook, Col. 4, lines 5-41. "Clinical effect" is normally used in the medical field to refer to signs or symptoms as observed in the clinic rather than those determined through laboratory tests. Even if Cook used the term "clinical effect" to include laboratory tests for relief of pain, it is in no way clear what sort of tests he may have implied because none are specifically indicated in Cook and none were in common use at the time. In fact, the most common test for relief of pain at the time of the Cook reference and even at present is a subjective test based on a patients' own rating of pain and detecting of readily apparent physical symptoms of severe pain, such as heart palpitations, sweating, etc. Such tests are described in the background of the present application. See Specification, page 2, lines 4-20.

Nevertheless, in the Office Action mailed April 8, 2003, the Examiner states "Cook discloses a method for diagnosing the intensity of pain in a patient comprising determining the amount of cholinesterase in a biological sample from the patient. See this entire document." See Office Action 4/8/03 page 2, item 5. The Examiner also makes various statements regarding the fact that Cook treats a demyelination disorder resulting from cholinesterase imbalance.

The alleged significance behind Cook's disclosure of treatment is explained further in an earlier Office Action of June 3, 2002. In that Office Action, the Examiner states "Cook further discloses methods for administering pharmaceutical compositions to alleviate pain associated with cholinesterase imbalance(s) in the patients with pathological central nervous system (i.e. brain and spine) or spinal cord conditions. Note column 5, lines 2-29, and

column 6, lines 1-28. Thus Cook discloses all the limitations claimed except for implicitedly [sic] stating that a 'predetermined pain marker amount' was used in the method. However, with respect to the use of a 'predetermined pain marker amount' in a comparison step, Cook discloses comparative evaluation was permitted during the diagnostic and therapeutic methods disclosed. See column 4, lines 2-5."

In a telephone interview with the Examiner on October 21, 2002, Applicants requested that the Examiner explain how the discussion of treatment in Cook implicitly discloses all of the steps of a method of diagnosis in Applicants' claims. She asserted that the statement "comparative evaluation was permitted" in Cook, Col. 4, lines 2-5 indicates that serum cholinesterase levels were measured in Cook's study population.

It therefore appears clear that the Examiner does not assert that Cook explicitly discloses a method or kit as claimed by the Application, but rather that such method or kit is implied by Cook. However, she has failed to comply with the requirements for asserting inherency as set forth in relevant case law and summarized in the MPEP.

b. The Inherency Standard and Analysis of the Examiner's Inherency Arguments

MPEP §2112 explicitly states that the "Examiner must provide a rationale or evidence tending to show inherency". More specifically, §2112 states:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)...; *In re Oelrich*, 666 F.2d 578, 581-21, 2212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however must not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted)... In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)(emphasis in original)

Applying the standards of MPEP 2112 to the Cook reference and the previous Office Actions, it appears that, at best, the Examiner has raised the possibility that Cook was

measuring cholinesterase in his patients. However, he did not *necessarily* measure it. He certainly did not *necessarily* measure it by the particular method described in Applicants' invention. Furthermore he did not *necessarily* make the comparisons described in Applicants' methods or *necessarily* use Applicants' kits. The comparisons the Examiner so heavily relies upon in Cook Col. 4, lines 2-5 are described in further detail in the following paragraph and relate to several symptoms of demyelinating diseases, Cook Col. 4., lines 5-41. None of these comparisons *necessarily* include measurement of cholinesterase. In fact, none of them even *probably* include it.

One comparison, that of pain relief among patient groups, appears to be the comparison upon which the Examiner most heavily relies for her rejections. Cook very clearly did not *necessarily* or even *probably* use the methods or kits of Applicants' invention to make this comparison. As described above, he most likely used a subjective test such as those detailed in Applicants' Specification, page 2, lines 4-20. Furthermore, Cook described in explicit detail any actual measurements that were available, such as dosages and time course of effectiveness. Cook, Col. 3, lines 53-62 and Col. 6, lines 8-46. It seems quite implausible that Cook would be precise regarding some objectively measurable data and then completely fail to include other measurements. Furthermore, as a review of any scientific literature and other patents in the medical and assay areas reveal, it is quite standard to include *any* actual quantitative results or to at least summarize them and provide an average or mean result. The Examiner's allegation that Cook performed quantitative tests such as those of the present invention and did not include the results in his patent is tantamount to alleging that he is an incompetent scientist who does not even know how to follow basic reporting standards. Furthermore, given that the Examiner has found no alleged prior art for the assay of the present invention other than Cook, Cook would have every incentive to disclose the assay and obtain patent protection for it himself. In summary, the Examiner's assertions regarding Cook are illogical in a number of ways and certainly do not show that Applicants' assay was necessarily used by Cook.

Therefore, the Examiner has failed to meet the burden for showing inherency set forth in MPEP §2112 because she has in no way indicated why Cook *necessarily* used a method or kit of the present invention in evaluating his novel treatments.

In addition to the inherency problems addressed above, the Examiner has failed to even allege that various limitations found in the claims are also found in Cook. The deficiencies are discussed in further detail below, but in summary they render an anticipation rejection of many of Claims 56, 60-62, 67, 76 and 82-85 inappropriate even if the Examiner's allegations regarding subject matter inherent in Cook are assumed to be correct. Such deficiencies are discussed below in reference to each appealed claim.

c. Specific §102(b) Analysis of the Claims

Claim 56 as amended recites a method of diagnosing the extent of activation of the pain sensing neurological pathway in a patient. This is accomplished by "determining the amount of a cholinesterase pain marker in a biological sample obtained from said patient, comparing the amount of the cholinesterase pain marker in said sample to a threshold amount of cholinesterase pain marker; and assign a pain status to the patient based on the comparison....". Cook does not determine the amount of cholinesterase in a biological sample and thus has nothing to compare to a threshold amount to assign a pain status. Furthermore, Claim 56 very specifically recites that "the threshold amount of cholinesterase pain marker is determined by measuring the amount of cholinesterase in samples from patients in whom the pain sensing neurological pathway is not activated and setting the threshold so that threshold amount of cholinesterase pain marker is at least three standard deviations above the mean cholinesterase amount in samples from normal individuals." Cook certainly does not provide such a detailed account of how to set a threshold amount, nor has the Examiner ever provided any allegation or reasoning to suggest that it does. Therefore, several limitations of Claim 56 are not present in Cook and Claim 56 is not anticipated by Cook.

Claim 60 is dependent upon Claim 56 and is therefore not anticipated by Cook for the reasons explained for Claim 56. Claim 60 adds the further limitation that "additional amounts of cholinesterase pain marker are identified as indicative of increasing levels of pain sensing neurological pathway activation by comparing the mean amount of cholinesterase pain marker in individuals with higher levels of pain sensing neurological pathway activation with mean cholinesterase pain marker in individuals with lower levels of pain sensing neurological activating and selecting an amount between the two means." The Examiner has

not alleged that Cook provides such a detailed account of identifying increasing levels of pain sensing neurological pathway activation, nor does Cook actually include anything so specific. Therefore Cook does not anticipate Claim 60.

Claim 61 is dependent upon Claim 56 and is therefore not anticipated by Cook for the reasons explained for Claim 56.

Claim 62 is dependent upon Claim 56 and is therefore not anticipated by Cook for the reasons explained for Claim 56. Claim 62 additionally indicates that "the sample is blood or serum and the cholinesterase is serum cholinesterase". Cook does not specifically describe the type of cholinesterase at issue, nor does the Examiner provide any reasoning why serum cholinesterase would be used. Therefore Cook does not include at least one limitation of Claim 62 and does not anticipate that claim.

Claim 67 is dependent upon Claim 56 and is therefore not anticipated by Cook for the reasons explained for Claim 56. Claim 67 additionally indicates that "the threshold amount of cholinesterase pain marker is based upon a normal individual sample obtained from the same patient prior to activation of the pain sensing neurological pathway." Again, the Examiner does not indicate that Cook contains this limitation. In fact, given that the patients described in Cook appear to be later stage neurodegenerative disease patients, it is highly unlikely that a sample of cholinesterase pain marker obtained before the onset of pain was even available. Cook therefore also fails to anticipate Claim 67.

Claim 76 is related to a "diagnostic kit for determining the level of action of the pain sensing neurological pathway in a patient". The kit includes "at least one antibody that binds to cholinesterase in a biological sample obtained from the patient wherein the amount of cholinesterase in the sample is then compared with an amount of cholinesterase known to be indicative of activation of the pain sensing neurological pathway." Cook does not disclose a kit and certainly does not discuss detection antibodies. The Examiner does not even appear to have alleged that it does. Therefore, Claim 76 is not anticipated by Cook.

Claim 82 is related to a "method of diagnosing the extent of activation of the pain sensing neurological pathway in a patient". The method includes "determining the amount of a pain marker in a biological sample obtained from said patient; comparing the amount of the pain marker in said sample to at least one pre-determine pain marker amount; and assigning a pain status to the patient based upon the comparison." Cook does not disclose determining

the amount of a pain marker in a biological sample and therefore cannot provide for comparison to a pre-determined amount followed by assigning a pain status. Therefore, Claim 82 is not anticipated by Cook.

Claim 83 is related to a "method of determining the efficacy of a treatment for pain". The method includes "determining the amount of a pain marker in a first biological sample obtained from said patient; administering the treatment to said patient; determining the amount of a pain marker in a second biological sample obtained from said treated patient; and comparing the amount of the pain marker in the first and second biological samples." Cook does not disclose determining the amount of a pain marker in a biological sample and therefore cannot provide for comparison before and after treatment. Therefore, Claim 83 is not anticipated by Cook.

Claim 84 is related to a "diagnostic kit for determining the level of activation of the pain sensing neurological pathway in a patient". The kit includes "at least one agent that reacts with cholinesterase in a biological sample obtained from a patient wherein the amount of cholinesterase in the sample is then compared with an amount of cholinesterase known to be indicative of activation of the pain sensing neurological pathway." Cook does not disclose a kit, nor does the Examiner allege that it does. Therefore, Claim 83 is not anticipated by Cook.

Claim 85 is related to a "method of diagnosing the extent of activation of the pain sensing neurological pathway in a patient". The method includes determining the amounts of at least two pain markers in a biological sample obtained from said patient; comparing the amounts of the at least two pain markers in said sample to a pre-determined amount of each pain marker; and assigning a pain status to the patient based upon the comparison." Cook does not disclose measuring even one pain marker, let alone two and also does not discuss comparison with a pre-determined amount and assignment of a pain status. The Examiner does not even appear to allege measurement of two pain markers. Therefore, Cook is not anticipated by Claim 84.

(2) Rejections under 35 U.S.C. § 103 (a)

a. Description of the Cook Reference and the Office Actions

Claims 56, 60-62, 67, 76, and 82-85 stand rejected under 35 U.S.C. § 103 (a) as being unpatentable over Cook.

A finding of obviousness under 35 U.S.C. §103(a) requires a demonstration of the scope and content of the prior art, the level of ordinary skill in the art, differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1996). The relevant inquiry is whether the prior art both suggests the invention and provides one of ordinary skill in the art with a reasonable expectation that the suggestion would work. *In re O'Farrell*, 853 F.2d 1549, 7 USPQ2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be found in the prior art and not in Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Because the Examiner has only cited Cook for the basis of her §103(a) rejections, all of these criteria must be satisfied by that reference alone. A detailed explanation of how the Claims are allegedly obvious in light of Cook as opposed to anticipated by the reference has never been provided. In all office actions, the claims have simply been rejected as anticipated by Cook or, in the alternative obvious in light of Cook. The Examiner's comments on these rejections have focused on the anticipation rejections. Therefore, it is not entirely clear to Applicants which claim limitations are allegedly obvious.

However, applying the considerations set forth in *Graham*, Applicants note that there is limited prior art relating to actual laboratory tests for pain. Most tests focus on reporting by the patient or clinically observable symptoms, such as sweating and heart palpitations. See Specification, page 2, lines 4-20. However, the relative level of skill in the art is high because of extensive technical or medical training required of most practitioners.

Numerous differences exist between the prior art and the present invention. As explained in much greater detail above, Applicants believe that Cook simply fails to teach or suggest any sort of measurement of a pain marker in a patient sample to determine activation of the pain sensing neurological pathway. Although Cook does note that his treatment reduces pain in patients with demyelinating disorders, this is indicated to be a "clinical"

observation, most likely made by asking the patient questions and conducting a physical examination. One skilled in art would not assume that Cook used some sort of laboratory test or kit such as those claimed by the Applicant.

Finally, Applicants submit that the differences between Cook and the invention are so great that one skilled in the art would not find them obvious. Specifically, one skilled in the art would likely not envision Applicants' methods and kits at all based on the Cook disclosure and certainly would not have any reasonable expectation of success, given the general lack of objective, quantitative assays for detecting activation of the pain sensing neurological pathway.

b. Specific §103(a) Analysis of the Claims

Claim 56 is directed to a method of detecting activation of the pain sensing neurological pathway and, as explained above, contains many claim limitations not present in Cook. Evan assuming that Cook discloses the step of "determining the amount of a cholinesterase pain marker in a biological sample", Cook certainly does not teach or suggest setting a threshold for comparison "so that the threshold amount of cholinesterase pain marker is at least three standard deviations above the mean cholinesterase amount in samples from normal individuals". Furthermore, it was not apparent until actual studies were conducted that three standard deviations above the normal amount of cholinesterase pain marker was the optimal amount to rule out false positives. Other levels of difference may have been optimal, or the cholinesterase pain marker levels between normal individuals and individuals in pain may have overlapped, making it impossible to rule out false positives without generating a number of false negatives. Accordingly, the method of threshold setting disclosed in Claim 56 is not obvious in light of Cook, even assuming the Examiner's assertions are otherwise true. Claim 56 is therefore not obvious in light of Cook.

Claim 60 is not obvious because it depends upon Claim 56, which is not obvious. Furthermore, Cook does not teach or suggest identifying additional amounts of cholinesterase pain marker "as indicative of increasing levels of pain sensing neurological pathway activation". One skilled in the art would not have expected to see measurable differences in amounts of cholinesterase pain marker as pain increases and to be able to use these to develop a scale. Therefore Claim 60 is not obvious in light of Cook.

Claims 61, 62 and 67 are not obvious because they depend upon Claim 56, which is not obvious.

Claim 76 is related to a diagnostic kit using an antibody that binds to cholinesterase and is not obvious in light of Cook because Cook does not teach or suggest measuring cholinesterase in a biological sample. Furthermore, assuming the Examiner's assertions regarding Cook are correct, it certainly does not disclose use of an antibody. Absent actual generation of any antibody, one would not have a reasonable expectation of success in producing an antibody useful in the diagnostic kit of Claim 76. Although antibody production is known, it is also axiomatic in the field that generation of specific stable antibodies to a given protein that are also useful in a given assay is not always possible. Therefore Claim 76 is not obvious in light of Cook.

Claim 82 is directed to a method of diagnosing activation of the pain sensing neurological pathway. Claim 82 includes the step of "determining the amount of a pain marker in a biological sample". Cook neither discloses nor suggests determining the actual amount of a pain marker for reasons explained above. Specifically, Cook likely used subjective questions and clinical techniques rather than laboratory tests to evaluate pain reduction in his patients. Therefore Claim 82 is not obvious in light of Cook.

Claim 83 is directed to a method for determining the efficacy of treatment for pain by "determining the amount of a pain marker in a first biological sample" and "determining the amount of a pain marker in a second biological sample" obtained after treatment and "comparing the amount of the pain marker in the first and second biological samples." Cook does not teach or suggest determining the amount of pain marker in a biological sample for reasons explained above. Specifically, Cook likely used subjective questions and clinical techniques rather than laboratory tests to evaluate the efficacy or his treatment in reducing pain. Therefore Claim 83 is not obvious in light of Cook.

Claim 84 is directed to a diagnostic kit for determining the level of activation of the pain sensing neurological pathway including "at least one agent that reacts with cholinesterase". Cook does not teach or suggest any use of agents to react with cholinesterase. Rather, Cook likely discloses the use of clinical techniques such as questions and observations to detect pain rather than use of an agent to react with cholinesterase. Therefore Claim 84 is not obvious in light of Cook.

Claim 85 is directed to a method of diagnosing the extent of activation of the pain sensing neurological pathway by "determining the amounts of at least two pain markers in a biological sample". Cook does not teach or suggest determining the amount of a pain marker. Rather, Cook likely relied upon clinical techniques such as questions and physical examinations to determine the pain status of his patients. Therefore Claim 85 is not obvious in light of Cook.

In light of the above arguments, Applicant respectfully submits that all of the claims are in condition for allowance over the Cook reference.

(3) Explanation of Independent Patentability of Claim Groups

All independent method claims (Claim 56, 82, 83, and 85) are independently patentable from the kit claims (Claims 76 and 84) because the kit claims include the use of an antibody or agent which is not specifically recited in the method claims. Although the method claims may use an antibody or agent to detect the relevant pain markers, they do not necessarily do so. Additionally, method Claim 56 recites a way of determining a threshold not implicit or explicit in the kit claims. Claims 82 and 83 recite particular uses, assigning a pain status and measuring efficacy of treatment, respectively. Although the kits of the kit claims may be used for these particular uses, they are not necessarily so limited. Claim 85 recites the measurement of two pain markers. Although the kits may be used to detect two pain markers, they do not necessarily have this capacity and may be used to detect only one pain marker.

Claim 56 is separately patentable from Claim 82 because Claim 56 specifies a detailed method or determining pain status while Claim 82 merely requires that a pain status be assigned. Claim 56 is separately patentable from Claim 83 because Claim 83 is directed to a method of determining the efficacy of treatment while Claim 56 includes assigning a pain status. One may determine the efficacy of treatment without ever assigning a pain status. Claim 56 is separately patentable from Claim 85 because Claim 85 recites a method of diagnosing the extent of activation of the pain sensing neurological pathway by detecting at least two pain markers. Claim 56 only requires detection of at least one pain marker.

Claim 76 is separately patentable from Claim 84 because Claim 84 only requires the use of an agent that reacts with cholinesterase in the kit while Claim 76 requires an antibody that binds to cholinesterase.

CONCLUSION

Applicant has demonstrated that the present invention as claimed is clearly distinguishable over all the art cited of record. Therefore, Applicant respectfully requests the Board of Patent Appeals and Interferences to reverse the final rejection of the Examiner and instruct the Examiner to issue a notice of allowance of all pending claims.

Applicant respectfully submits this appeal brief with a check in the amount of $160.00 to cover the cost of filing an appeal brief under 37 C.F.R. § 1.192 and § 1.17(c). The Commissioner is hereby authorized to charge any fees or credit any overpayment to Deposit Account No. 50-2148 of Baker Botts L.L.P.

Respectfully submitted,
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CURRENT CLAIMS

21. A method for identifying a marker that correlates with the intensity of a pain perceived by a patient comprising the steps of:

collecting a serum sample from the patient;

separating the components within said serum sample by electrophoresis in a gel;

reacting the gel with a diazonium salt and a substrate for a period of time to form a detectable band comprising an insoluble diazonium complex; and

identifying the size and location of the detectable band to identify said marker.

22. The method of claim 21 wherein the gel has a gradient polymer density.

23. The method of claim 21 wherein the diazonium salt is 4-chloro-2-methylaniline.

24. The method of claim 21 wherein reacting is terminated by adding a reagent to the gel wherein said reagent is selected from the group consisting of acetic acid, formic acid and citric acid and mixtures thereof.

25. The method of claim 21 further comprising performing densitometry analysis on said gel.

Claims 26-55 were previously cancelled without prejudice or disclaimer.

Please cancel claims 57-59, 68, 71-75, 77 and 79-80 without prejudice of disclaimer.

Please amend the claims indicated below as follows:

56. (Once Amended) A method of diagnosing the extent of activation of the pain sensing neurological pathway in a patient comprising:

i) determining the amount of a cholinesterase pain marker in a biological sample obtained from said patient;

ii) comparing the amount of the cholinesterase pain marker in said sample to a threshold amount of cholinesterase pain marker; and

iii) assigning a pain status to the patient based upon the comparison, wherein the threshold amount of cholinesterase pain marker is determined by measuring the amount of cholinesterase in samples from patients in whom the pain sensing neurological pathway is not activated and setting the threshold so that the threshold amount of cholinesterase pain marker is at least three standard deviations above the mean cholinesterase amount in samples from normal individuals.

60. (Once Amended) The method of claim 56, wherein additional amounts of cholinesterase pain marker are identified as indicative of increasing levels of pain sensing neurological pathway activation by comparing the mean amount of cholinesterase pain marker in individuals with higher levels of pain sensing neurological pathway activation with mean of cholinesterase pain marker in individuals with lower levels of pain sensing neurological pathway activation and selecting an amount between the two means.

61. (Previously Added) The method of claim 56, wherein the pain sensing neurological pathway is activated by chronic spinal pain.

62. (Previously Added) The method of claim 61, wherein the sample is blood or serum and the cholinesterase is serum cholinesterase.

63. (Previously Added) The method of claim 62, wherein threshold amount of cholinesterase pain marker is 1272 and patients from whom the sample contains less than this amount of serum cholinesterase are deemed to have normal activation levels of the pain sensing neurological pathway while patients from whom the sample contains greater than this amount of serum cholinesterase are deemed to have high or activated activation levels of the pain sensing neurological pathway.

64. (Previously Added) The method of claim 56 further including the step of separating components within the biological sample.

65. (Previously Added) The method of claim 64 wherein separating comprises an electrophoretic separation.

66. (Once Amended) The method of claim 56, wherein the cholinesterase in the biological sample is reacted with a substrate to produce a detectable product.

67. (Once Amended) The method of claim 56, wherein the threshold amount of cholinesterase pain marker is based upon a normal individual sample obtained from the same patient prior to activation of the pain sensing neurological pathway.

69. (Previously Added) The method of claim 56 , wherein the activation of the pain sensing neurological pathway is caused by the presence of a lesion.

70. (Once Amended) The method of claim 56, whereby cholinesterase is distinguished and measured by eserine sensitivity.

76. (Once Amended) A diagnostic kit for determining the level of activation of the pain sensing neurological pathway in a patient comprising at least one antibody that binds to cholinesterase in a biological sample obtained from the patient wherein the amount of cholinesterase in the sample is then compared with an amount of cholinesterase known to be indicative of activation of the pain sensing neurological pathway.

78. (Once Amended) The diagnostic kit of claim 76, wherein the antibody or antibodies are polyclonal antibodies, monoclonal antibodies or fragments of polyclonal or monoclonal antibodies.

81. (Previously Added) The method of claim 76 wherein cholinesterase is distinguished and measured based upon eserine sensitivity.

Please add new claims 82-85 as follows:

82. (New) A method of diagnosing the extent of activation of the pain sensing neurological pathway in a patient comprising:

i) determining the amount of a pain marker in a biological sample obtained from said patient;

ii) comparing the amount of the pain marker in said sample to at least one pre-determined pain marker amount;

iii) assigning a pain status to the patient based upon the comparison.

83. (New) A method for determining the efficacy of a treatment for pain comprising:

i) determining the amount of a pain marker in a first biological sample obtained from said patient;

ii) administering the treatment to said patient;

iii) determining the amount of a pain marker in a second biological sample obtained from said treated patient; and

iv) comparing the amount of the pain marker in the first and second biological samples.

84. (New) A diagnostic kit for determining the level of activation of the pain sensing neurological pathway in a patient comprising at least one agent that reacts with cholinesterase in a biological sample obtained from a patient wherein the amount of cholinesterase in the sample is then compared with an amount of cholinesterase known to be indicative of activation of the pain sensing neurological pathway.

85. (New) A method of diagnosing the extent of activation of the pain sensing neurological pathway in a patient comprising:

i) determining the amounts of at least two pain markers in a biological sample obtained from said patient;

ii) comparing the amounts of the at least two pain marker in said sample to a pre-determined amount of each pain marker

iii) assigning a pain status to the patient based upon the comparison.